An integro-differential equation for 1D cell migration

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1.1 Introduction

Cell migration is a fundamental biological phenomenon involved for example in development, wound healing, cancer and immune response. Understanding its key features is therefore a burning issue.

Some cells can move on an adherent substrate by a *crawling* process, where motion comes from the formation of finger-like extensions named *filopodia* that adhere to the substrate for some time. When the cell contracts, non-adherent filopodia retract, whereas adherent ones exert forces that induce motion. We refer to [AnEh07] for a complete description of cell crawling.

When a cell is set on a flat homogenous substrate, it performs a random-like motion. However, it can also become polarized and move in a preferential direction. How this direction is chosen is a question that is still driving many experimental and modeling efforts. In [CaVoRi14], a non-homogenous substrate impose geometrical constraints that are sufficient to direct 1D cell motion. This paper focuses on the 1D motion brought forth by the filopodial activity.

We introduce a simplified model of 1D cell migration relying on the filopodial activity. In what follows, the substrate is supposed to be flat and homogenous, but more complex settings could also be described. Let us consider the center of mass of the cell, whose position at time t is denoted $x(t) \in \mathbb{R}$. Force equilibrium leads to

$$C\frac{dx}{dt}(t) = -F_\ell(t) + F_r(t), \tag{1.1}$$

where $F_r \geq 0$ (resp. $F_\ell \geq 0$) is the force exerted by filopodia located on the right (resp. on the left) of the cell and C is the friction parameter, that can be set equal to $1nN.h.\mu m^{-1}$ [WoTa11].

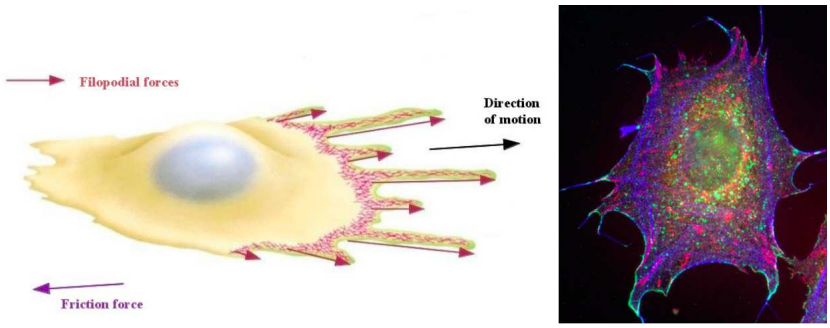

Fig. 1.1. Illustration of a moving cell, and picture of a fibroblast [MaSiBrYeMe08].

We can now focus on the forces $F_{r,\ell}$. Following biological knowledge, we assume that the forces exerted by filopodia on the cell at time t depend on:

- densities of filopodia sent to the right and left, denoted by $\psi_{r,\ell} > 0$,
- their existence time, fixed by the lifetime function $\mathcal{P} : \mathbb{R}^+ \to \mathbb{R}^+$,
- the force $f_{r,\ell}$ exerted by one filopodium on the cell, related to its orientation. Moreover, we assume that $f_{r,\ell} = f_{r,\ell}(x(t'), x(t))$ depends on the positions of both the tip of the filopodium, related to the cell position at creation time t', and the actual cell position.

Consequently, equation (1.1) rewrites as an integro-differential equation

$$\begin{aligned} &\frac{dx}{dt}(t) = \int_0^t \mathcal{P}(a)\Big(\psi_r f_r(x(t-a), x(t)) - \psi_\ell f_\ell(x(t-a), x(t))\Big)da, \qquad (1.2)\\ &x(0) = x_0, \end{aligned}$$

where $\psi_{r,\ell}$ are positive constants, $x : \mathbb{R}^+ \to \mathbb{R}$, and $f_{r,\ell} : \mathbb{R}^2 \to \mathbb{R}$. Let us assume for simplicity that $x_0 = 0$.

Problem (1.2) can be treated more or less easily depending on the force functions $f_{r,\ell}$. In this work, we shall first investigate one case of non-linear elastic force, where only existence and uniqueness of a solution can be proved. Then, we shall consider a simplified case of linear force functions, where a linear Volterra equation can be obtained. We shall see how this formalism allows us to get more information on the sign, boundedness and asymptotic behaviour of the solution in general, as well as explicit solutions for some special cases.

1.2 Non-linear force functions

Let us start with the force functions

$$f_r(y, x) = k\,[\ell - (x - y)]_+\,, \quad \text{and} \quad f_\ell(y, x) = k\,[\ell - (y - x)]_+\,,$$

where $[.]_+$ denotes the positive part function and $k, \ell \in \mathbb{R}^+$ are two constants. Taking $f_r(x(t-a), x(t))$ and $f_\ell(x(t-a), x(t))$, it corresponds to the hypothesis of filopodia having a constant size ℓ, and exerting elastic forces as long as the cell at position $x(t)$ has not reached their tips $x(t-a) \pm \ell$. Equation (1.2) now writes

$$\begin{aligned}\frac{dx}{dt}(t) = k \int_0^t \mathcal{P}(a)\Big(\psi_r[\ell + x(t-a) - x(t)]_+ \\ - \psi_\ell\left[\ell + x(t) - x(t-a)\right]_+\Big)da.\end{aligned} \tag{1.3}$$

1.2.1 Existence and uniqueness

We prove the following result :

Theorem 1. *For $\mathcal{P} \in L^1(\mathbb{R}^+)$, there exists a unique solution $x \in \mathcal{C}^1(\mathbb{R}^+, \mathbb{R})$ of (1.3).*

Proof. After integration, equation (1.3) writes

$$\begin{aligned}x(t) = k \int_0^t \int_0^s \mathcal{P}(a)\Big(\psi_r\big[x(s-a) + \ell - x(s)\big]_+ \\ - \psi_\ell\big[x(s) - x(s-a) + \ell\big]_+\Big)dads =: \Phi(x)(t)\end{aligned}$$

with

$$\begin{aligned}\Phi : \big(\mathcal{C}([0,T],\mathbb{R}), \|\ \|_\infty\big) &\longrightarrow \big(\mathcal{C}([0,T],\mathbb{R}), \|\ \|_\infty\big) \\ x &\longmapsto \Phi(x) = (t \mapsto \Phi(x)(t)),\end{aligned}$$

for some $T \geq 0$. We are looking for existence and uniqueness of a fixed point for Φ. Let us construct a sequence $(x^n)_{n\geq 0}$ in $\mathcal{C}([0,T],\mathbb{R})$ such that

$$x^0 \equiv x_0, \quad x^{n+1} = \Phi(x^n)\ \forall n \geq 0.$$

As $[0,T]$ is compact, $\big(\mathcal{C}([0,T],\mathbb{R}), \|\ \|_\infty\big)$ is a Banach space and we can use the Banach fixed-point theorem. All we need to show now is that Φ is a contraction mapping. Considering $(y,z) \in \big(\mathcal{C}([0,T],\mathbb{R}), \|\ \|_\infty\big)^2$ and denoting

$$g_{s,a}(y) = y(s-a) + \ell - y(s), \quad \text{and} \quad h_{s,a}(y) = y(s) - y(s-a) + \ell,$$

we have

$$\begin{aligned}\|\Phi(y) - \Phi(z)\|_\infty = \sup_{t\in[0,T]} \Bigg| k \int_0^t \int_0^s \mathcal{P}(a)\Big(\psi_r\big([g_{s,a}(y)]_+ - [g_{s,a}(z)]_+\big) \\ - \psi_\ell\big([h_{s,a}(y)]_+ - [h_{s,a}(z)]_+\big)\Big)dads\Bigg| \\ \leq kT \sup_{s\in[0,T]} \int_0^s |\mathcal{P}(a)| \times \Big(\psi_r\big|[g_{s,a}(y)]_+ - [g_{s,a}(z)]_+\big| \\ + \psi_\ell\big|[h_{s,a}(y)]_+ - [h_{s,a}(z)]_+\big|\Big)da,\end{aligned}$$

since $\psi_{r,\ell} \geq 0$. Denote $\psi := \psi_r + \psi_\ell$. Now, for $(A, B) \in \mathbb{R}^2$, the inequality $\big|[A]_+ - [B]_+\big| \leq \big|A - B\big|$ holds, leading to

$$\begin{aligned} \| \Phi(y) - \Phi(z) \|_\infty &\leq kT \sup_{s\in[0,T]} \int_0^s \psi \, |\mathcal{P}(a)| \, \big|(y-z)(s-a) - (y-z)(s)\big| da, \\ &\leq 2kT\psi \, \| \mathcal{P} \|_{L^1(\mathbb{R}+)} \| \, y - z \, \|_\infty \, . \end{aligned}$$

For T small enough such that $2k\psi \, \| \, \mathcal{P} \, \|_{L^1(\mathbb{R}+)} \, T < 1$, we deduce that Φ is a contraction mapping. As a consequence of the Banach fixed-point theorem, there exists a unique $x \in \mathcal{C}([0,T], \mathbb{R})$ which is solution of (1.3).

Iterating the same reasoning on time intervals of size T, one can extend this result to prove that (1.3) admits a unique solution $x \in \mathcal{C}(\mathbb{R}^+, \mathbb{R})$. Finally, using (1.3), it is clear that $x \in \mathcal{C}^1(\mathbb{R}^+, \mathbb{R})$, and this concludes the proof.

1.2.2 Numerical simulations

We consider the lifetime function $\mathcal{P} : a \mapsto e^{-a}$. This means that a density of filopodia will exponentially decrease with time, as more and more filopodia will have disappeared. For the filopodia's length, we use an experimental value from [CaVoRi14]. Moreover, we impose a bias on the densities of filopodia ($\psi_r > \psi_\ell$).

Figure 1.2 represents the cell position and velocity over time computed with an explicit Euler time discretization and a rectangle integration method of equation (1.3). What can be observed is that the bias in the produced forces seems to lead to a non-zero asymptotic velocity. Further simulations with different parameter values and/or lifetime functions confirm this tendency.

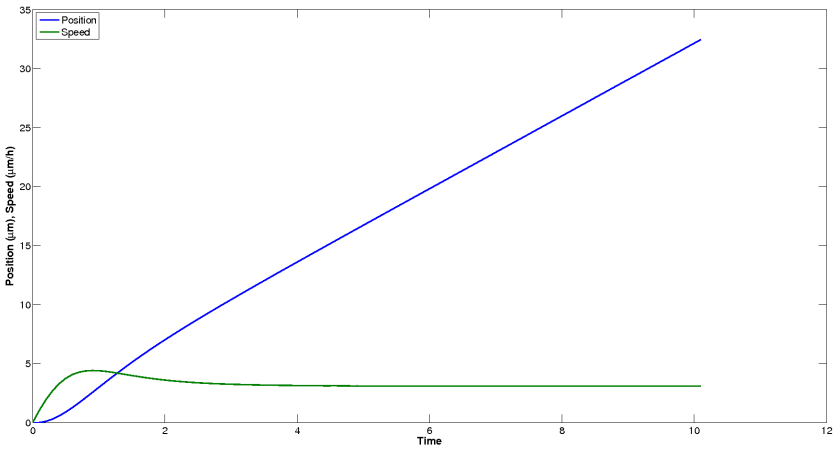

Fig. 1.2. Numerical simulation of a particle speed and trajectory during $T = 10h$, for $dt = 10^{-2}h$, $C = 1nN.h.\mu m^{-1}$, $k = 1nN.\mu m^{-1}$, $\ell = 20.5\mu m$, and $(\psi_r, \psi_\ell) = (1.5, 1)$.

1.3 Linear forces

The presence of the positive part function in the previous case prevents getting analytical properties of the solution. In this section, we will take the following linearized forces functions:

$$f_r(x(t-a), x(t)) = k\left(x(t-a) + \ell - x(t)\right),$$
$$f_\ell(x(t-a), x(t)) = k\left(x(t) - x(t-a) + \ell\right),$$

with $k, \ell \in \mathbb{R}^+$. This assumption is less relevant from the modelling point of vue, since if the cell overtakes the tip of a filopodium, then it will experience a force in the opposite direction. However, for k small enough, and an appropriate lifetime function, we can assume that the cell is slow enough so that it does not reach any existing filopodium tip.

Equation (1.2) can be written as a linear Volterra equation, which will lead to more analytical results.

1.3.1 Linear Volterra equation formalism

Let us rewrite equation (1.2):

$$\begin{aligned} v(t) &= k\int_0^t \mathcal{P}(a)\Big(\psi_r(x(t-a) + l - x(t)) - \psi_\ell(x(t) - x(t-a) + \ell)\Big)da \\ &= kl(\psi_r - \psi_\ell)\int_0^t \mathcal{P}(a)da + k\psi\int_0^t \mathcal{P}(a)\left(x(t-a) - x(t)\right)da. \end{aligned} \tag{1.4}$$

Denoting $Q : t \mapsto \displaystyle\int_0^t \mathcal{P}(a)da$ and integrating by parts, we obtain

$$v(t) = k\ell(\psi_r - \psi_\ell)Q(t) + k\psi\bigg(\int_0^t Q(a)v(t-a)da - Q(t)x(t)\bigg),$$

since $Q(0) = 0$ and $x(0) = 0$. After the change of variable $s = t - a$, we get

$$v(t) = f(t) - k\psi\int_0^t (Q(t) - Q(t-s))v(s)ds, \tag{1.5}$$

$$\text{with} \quad f(t) = k\ell(\psi_r - \psi_\ell)Q(t). \tag{1.6}$$

which is a linear Volterra integro-differential equation on v.

1.3.2 Existence and uniqueness of a solution

With similar arguments to Theorem 1, we can prove the following property:

Theorem 2. *For $\mathcal{P} \in L^1(\mathbb{R}^+)$, equation (1.5) admits a unique solution $v \in \mathcal{C}(\mathbb{R}^+, \mathbb{R})$.*

Remark 3 (The resolvent formalism) *Let us define the operator*

$$h \star v : t \mapsto \int_0^{+\infty} h(t,s)v(s)ds.$$

Equation (1.5) can then be written as a convolution-like equation:

$$\begin{aligned} &v(t) + (h \star v)(t) = f(t), \ \textit{with} \\ &h(t,s) = k\psi(Q(t) - Q(t-s))\mathbf{1}_{[0,t]}(s). \end{aligned}$$

Existence and uniqueness of a solution can be proved by showing that h is a Volterra kernel of L^∞ type. For more details, we refer to [GrLoSt90].

1.3.3 Sign and boundedness property

We now prove a result showing how important the function f is in controlling the migration. Indeed, it captures no less than the range of forces exerted with k, aging, and the potential asymmetry $\psi_r - \psi_\ell$ in the formation of filopodia.

Theorem 4. *If $\mathcal{P}$ is positive and decreasing, then the solution to equation* (1.5) *satisfies*

$$\begin{aligned} \psi_r \geq \psi_\ell \quad &\Rightarrow \quad \forall t \geq 0, \ v(t) \in [0, f(t)], \\ \psi_r \leq \psi_\ell \quad &\Rightarrow \quad \forall t \geq 0, \ v(t) \in [f(t), 0]. \end{aligned}$$

Proof. First, let us assume that $\psi_r \geq \psi_\ell$. As a consequence, $\forall t \geq 0, \ f(t) \geq 0$ and $f'(t) \geq 0$. By derivation of (1.5), we obtain

$$v'(t) = f'(t) - k\psi(Q(t) - Q(0))v(t) - k\psi \int_0^t (\mathcal{P}(t) - \mathcal{P}(t-s))v(s)ds,$$

with $f'(t) = k\ell(\psi_r - \psi_\ell)\mathcal{P}(t)$. Suppose there exists t^* such that $\forall t < t^*, \ v(t) > 0$ and $v(t^*) = 0$, then

$$v'(t^*) = f'(t^*) - k\psi Q(t^*)v(t^*) - k\psi \int_0^{t^*} (\mathcal{P}(t^*) - \mathcal{P}(t^* - s))v(s)ds$$

is positive (since all the terms are positive). Consequently, $\forall t \geq 0, \ v(t) \geq 0$. This implies that $x(t-a) - x(t) \leq 0, \forall t \geq a \geq 0$. Going back to the equivalent equation (1.4), this shows that $\forall t \geq 0, \ v(t) \leq f(t)$. Now, let us assume that $\psi_\ell \geq \psi_r$, which means that $\forall t \geq 0, \ f(t) \leq 0$ and $f'(t) \leq 0$. In a similar way, if there exists t^* such that $\forall t < t^*, \ v(t) < 0$ and $v(t^*) = 0$, then $v'(t^*)$ is negative. And considering again (1.4), we easily show that $\forall t \geq 0, \ v(t) \geq f(t)$, which concludes the proof.

1.3.4 Asymptotic velocity

We now give an expression for the asymptotic velocity of the cell. Here again, f has a crucial importance. The proof of the following result is similar to the one done in a forthcoming work [GrMaMeNa], and we do not repeat it here.

Theorem 5. *Let v be the solution of (1.5), and denote $\gamma = \lim_{t\to+\infty} f(t)$. Assume that v is uniformly continuous on $\mathbb{R}^+$. Then,*

$$v(t) \underset{t\to+\infty}{\longrightarrow} v_\infty = \begin{cases} \frac{\gamma}{1+k\psi\int_0^{+\infty} a\mathcal{P}(a)da} & \text{if } a \mapsto a\mathcal{P}(a) \in L^1(\mathbb{R}^+), \\ 0 & \text{if } a \mapsto a\mathcal{P}(a) \notin L^1(\mathbb{R}+). \end{cases}$$

Having two different cases can be interpreted as follows: if the mean lifetime of filopodia is finite, then the cell is permanently escaping from the action of older forces. As a consequence, if $\psi_r - \psi_\ell \neq 0$, it can get off its position all the time. However, if the mean lifetime of filopodia is infinite, all of them exert elastic forces on the cell, which will be stabilized in finite time.

1.3.5 Particular cases

Some choices of function $\mathcal{P}$ can give more explicit information on the solution.

Infinite existence time of forces ($\mathcal{P} \equiv 1$).

Taking $\mathcal{P} \equiv 1$, we are considering elastic forces that never disappear. Here, $\mathcal{P}$ does not fulfill the hypothesis of Theorem 2, but Theorem 5 applies. Equation (1.5) writes

$$v(t) = k\ell(\psi_r - \psi_\ell)t - k\psi\int_0^t sv(s)ds,$$

and can be solved after derivation with the variation of constants method, to give

$$v(t) = v(0)e^{-k\psi t^2/2} + \ell\sqrt{\frac{k\pi}{2}}(\psi_r - \psi_\ell)\sqrt{e^{-\frac{k\psi t^2}{2}}\left(1 - e^{-\frac{k\psi t^2}{2}}\right)}. \tag{1.7}$$

Figure 1.3 represents the solution v as well as the corresponding forcing function f. As expected, the cell is stabilized in finite time. Moreover, we can observe numerically the sign and boundedness property (given in Theorem 4), where in this case the $f(t)$ bound is optimal.

It is easy to check analytically the convergence of v to $v_\infty = 0$ since we have the following equivalence:

$$v(t) \underset{t\to+\infty}{\sim} \ell\sqrt{\frac{k\pi}{2}}(\psi_r - \psi_\ell)e^{-k\psi t^2/4}.$$

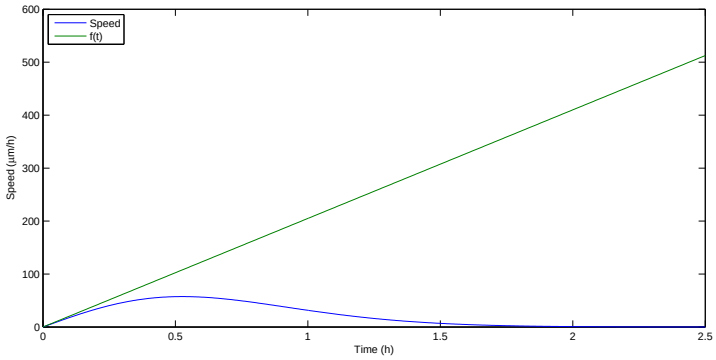

Fig. 1.3. Graph of $t \mapsto v(t)$ and $t \mapsto f(t)$ for $\mathcal{P} \equiv 1$, with $C = 1nN.h.\mu m^{-1}$, $\ell = 20.5\mu m$, $k = 5nN.\mu m^{-1}$, $(\psi_r, \psi_\ell) = (6, 4)$ and $v(0) = 0$.

Exponential decay ($\mathcal{P}(a) = e^{-a}$)

We assume now that $\mathcal{P}(a) = e^{-a}$, which was the function chosen in Section 1.2.2. All the results demonstrated before apply. However, we can actually directly solve the equation. Noting that $Q(t) = 1-e^{-t}$, equation (1.5) becomes

$$v(t) = k\ell(\psi_r - \psi_\ell)(1 - e^{-t}) - k(\psi_r + \psi_\ell)e^{-t}A(t), \tag{1.8}$$
$$\text{with} \quad A(t) = \int_0^t (e^s - 1)v(s)ds.$$

Proposition 1. *The solution to* (1.8) *is given by:*

$$v(t) = k\ell(\psi_r - \psi_\ell)\left(1 - e^{-t}\right) - k^2 l(\psi_r - \psi_\ell)\psi e^{-(k\psi+1)t+k\psi-k\psi e^{-t}}J(t), \tag{1.9}$$
$$\textit{with} \quad J(t) = \int_0^t (e^s + e^{-s} - 2)e^{k\psi(s-1+e^{-s})}ds.$$

Proof. Deriving A with respect to time leads to:

$$A'(t) = k\ell(\psi_r - \psi_\ell)(e^t + e^{-t} - 2) - k\psi(1 - e^{-t})A(t).$$

Now, by the variation of constant method, we find

$$A(t) = k\ell(\psi_r - \psi_\ell)e^{-k\psi(t-1+e^{-t})}\int_0^t (e^s + e^{-s} - 2)e^{k\psi(s-1+e^{-s})}ds,$$

leading to expression (1.9).

As a consequence, an asymptotic equivalent of the solution can be given.

Theorem 6. *The following equivalence holds:*

$$v(t) \underset{t\to+\infty}{\sim} k\ell(\psi_r - \psi_\ell)\left(1 - \frac{k\psi}{k\psi+1} - \frac{k\psi}{k\psi-1}e^{-2t} + 2e^{-t}\right), \tag{1.10}$$

and v converges to the asymptotic velocity

$$v_\infty := k\ell(\psi_r - \psi_\ell)\left(1 - \frac{k\psi}{k\psi+1}\right).$$

Proof. Using the following equivalence

$$\int_0^t e^{\alpha s} ds \underset{t\to+\infty}{\sim} \frac{e^{\alpha t}}{\alpha},$$

we easily obtain

$$J(t) \underset{t\to+\infty}{\sim} e^{-k\psi}\left(\frac{e^{(k\psi+1)t}}{k\psi+1} + \frac{e^{(k\psi-1)t}}{k\psi-1} - 2\frac{e^{k\psi t}}{k\psi}\right).$$

Considering expression (1.9), we have :

$$v(t) \underset{t\to+\infty}{\sim} kl(\psi_r - \psi_\ell)\left[1 - k\psi e^{-(k\psi+1)t}\left(\frac{e^{(k\psi+1)t}}{k\psi+1} + \frac{e^{(k\psi-1)t}}{k\psi-1} - 2\frac{e^{k\psi t}}{k\psi}\right)\right],$$

which leads to the result.

We can then deduce that the asymptotic behaviour of the cell depends on the range of filopodial forces k, on the global filopodial activity ψ, and on the asymmetry $\psi_r - \psi_\ell$. Moreover, the bigger k and ψ are, the faster the cell velocity reaches equilibrium. The non-trivial equilibrium is a consequence of the lifetime function that lets newer forces lead motion, whereas the older ones are "silenced". The initial asymmetry is then maintained over time. On Figure 1.4, a numerical simulation illustrates this behaviour.

Constant existence time ($\mathcal{P}(a) = 1_{[0,\tau]}(a)$)

Now, let us look at $\mathcal{P}(a) = 1_{[0,\tau]}(a)$ with $\tau > 0$, meaning that all filopodia exert forces during the same finite amount of time. For $t \geq 0$, we have

$$Q(t) = \begin{cases} t & \text{if } t < \tau, \\ \tau & \text{if } t \geq \tau. \end{cases}$$

Existence and uniqueness of a continuous solution to (1.5) comes from Theorem 2. Moreover, we can find an explicit solution for $t \leq \tau$, and bounds for the solution for $t \geq \tau$. Equation (1.5) then writes

$$v(t) = k\ell(\psi_r - \psi_\ell)t - k\psi\int_0^t sv(s)ds, \qquad \text{for } t \leq \tau, \tag{1.11}$$

$$v(t) = k\ell\tau(\psi_r - \psi_\ell) - k\psi\int_{t-\tau}^t v(s)(\tau - (t-s))ds, \qquad \text{for } t \geq \tau. \tag{1.12}$$

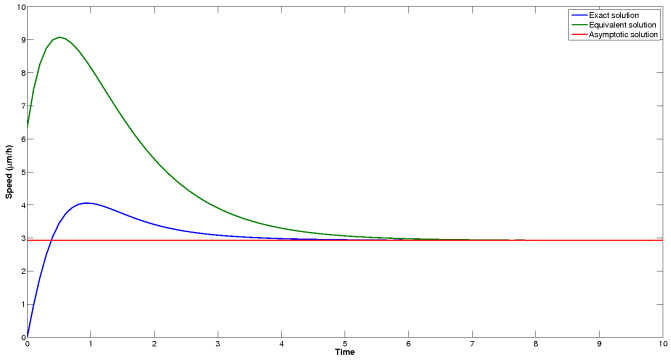

Fig. 1.4. Numerical simulation of the exact solution, its equivalent at infinity and the asymptotic velocity for $C = 1nN.h.\mu m^{-1}$, $k = 1nN.\mu m^{-1}$, $\ell = 20.5\mu m$ and $(\psi_r, \psi_\ell) = (1.5, 1)$.

Theorem 7. *The unique solution to equations (1.11)-(1.12) satisfies*

$$v(t) = \ell(\psi_r - \psi_\ell)\sqrt{\frac{k\pi}{2\psi}}\sqrt{(1 - e^{\frac{-k\psi}{2}t^2})} \qquad \text{for } t \leq \tau, \tag{1.13}$$

$$v(\tau)\exp\left(-k\psi\frac{(t^2-\tau^2)}{2}\right) \leq v(t) \leq k\ell(\psi_r - \psi_\ell) \qquad \text{for } t \geq \tau. \tag{1.14}$$

Proof. Let us first study the case where $t \leq \tau$. By derivation of (1.11), we have:

$$v'(t) = k\ell(\psi_r - \psi_\ell) - k\psi t v(t),$$

and the variation of constant method leads to expression (1.11).

Let us now consider the case where $t \geq \tau$. After a change of variable, equation (1.12) becomes

$$v(t) = k\ell\tau(\psi_r - \psi_\ell) - k\psi\int_0^\tau (\tau - s)v(t-s)ds, \tag{1.15}$$

$$= k\ell\tau(\psi_r - \psi_\ell) - k\psi\int_0^t (t - s)v(t-s)ds + h(t), \tag{1.16}$$

with

$$h(t) = k\psi\int_\tau^t (t-s)v(t-s)ds + k\psi\int_0^\tau (t-\tau)v(t-s)ds.$$

Since $\mathcal{P}$ is positive and decreasing, we deduce from Theorem 4 that $\forall t \geq 0,\ v(t) \geq 0$. Hence, we know that $h \geq 0$ on $[\tau, +\infty[$. Moreover, derivating h in t, we obtain

$$h'(t) = k\psi \left(\int_\tau^t \frac{d}{dt}((t-s)v(t-s))ds + \int_0^\tau \frac{d}{dt}((t-\tau)v(t-s))ds \right),$$
$$= k\psi \left((t-\tau)v(t) + (x(t) - x(t-\tau)) \right) \geq 0,$$

as $v \geq 0$. Then, derivating equation (1.16) leads to

$$v'(t) \geq -k\psi t v(t),$$

from which we deduce

$$v(t) \geq v(\tau) \exp\left(-k\psi \frac{(t^2 - \tau^2)}{2} \right),$$

leading to the first inequality. Moreover, as $v \geq 0$, the second one is obtained from equation (1.15), and this concludes the proof.

1.4 Conclusions and perspectives

In this paper, we have introduced a simple deterministic model of 1D cell migration, based on the filopodial activity of the cell. It describes the formation of antagonist elastic forces by filopodia on each side of the cell.

This model is not able to describe realistic trajectories, as the filopodial activity is taken constant, but it relates explicitly filopodial statistics to the cell velocity and asymptotic behavior, and hence represents a first step in the global description of cell trajectories from filopodial activity.

In this work, we have studied a realistic case where filopodia stop exerting a force as soon as the cell has overtook their tips. In this case, the highly nonlinear force prevent us from getting more than an existence and uniqueness result.

The case of linear elastic forces is richer, as it gave more information about the sign, boundedness and asymptotic behaviour of the solution. It is important to keep in mind that the linear model is realistic only in a particular setting: if the cell is slow enough, and filopodia's lifetime short enough, then they won't be reached by the cell. Typical velocity and filopodium lifetime are closely related to the cell type and experimental setting. Indeed, considering the force $k\ell$ exerted by a filopodium of length ℓ on the substrate, it is known that ℓ is variable among cell types. Moreover, k highly depends on the rigidity of the substrate: the more it is rigid, the larger the forces are [LoWaDeWa00]. Another key-player in the filopodial forces is the adhesiveness of the substrate, that scales how strong it is coupled to filopodia, hence how large forces will be. However, a very adherent substrate is also less likely to let go of filopodia during the contraction of the cell, leading to a longer lifetime for them. This results in a bell-shaped curve relating velocity and adhesiveness, as described in [PaLoHo97]. As a consequence, it is likely that for a substrate of low (or very large) adhesiveness and low rigidity, cells velocity would be low

enough so that the linear model fits with experimental conditions. This first-step model describing filopodial activity and trajectories is simple enough to give analytical information about the cell velocity, but still rich enough to be compared to different kinds of experimental 1D migration assays. In future works, it will be crucial to consider non constant densities of filopodia, to take into account the effect of motion itself on the filopodial activity. This would probably lead to much more realistic trajectories, where changes of direction would be described.

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